

Bronchial, Alveolar, and Vascular-Induced Anaphylaxis and Irritant-Induced Cardiovascular and Pulmonary Responses

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We examine the respiratory, bronchomotor, cardiac, and vascular responses to histamine and ragweed allergen delivered to the bronchi or alveoli compartments and the potential role of sensory nerves and reflexes mediating the histamine-induced responses. The masses of aerosols deposited in the bronchi and alveoli were quantitated using radioaerosol techniques. Activation of sensory nerves and/or histamine-induced mediator release were characterized by depositing nedocromil sodium aerosol prior to histamine challenge. The histamine-induced responses due to vagosympathetic transmission were determined by performing bilateral vagotomy. Both histamine and ragweed increased respiratory rate, ventilation, and bronchomotor tone whether deposited in the bronchial or alveolar regions. However, these responses were not elicited when histamine was administered intravenously. Precipitous allergen-induced decreases in heart rate and systolic and diastolic pressure were maximal 72 sec following ragweed deposition in alveolar regions of the lungs. Increases in respiratory rate were mediated via the vagus whether delivered to the bronchi, alveoli, or vasculature. Histamine-induced increases in respiratory rate and bronchomotor tone were attenuated by nedocromil. When histamine was delivered to the alveolar regions, increases in lung resistance appeared to be mediated primarily via the vagus and when delivered to the bronchial airways primarily by its action on smooth muscle or local reflexes. Histamine-induced hypotension and bradycardia appear to be mediated by the direct action of histamine on the cardiovascular system rather than through a vagally mediated reflex. **Key words:** histamine, nedocromil, neural pathways, pulmonary chemoreflex, ragweed. — *Environ Health Perspect* 109(suppl 4):513–522 (2001).

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Inhaled irritants and allergens initiate a pulmonary chemoreflex that can result in responses both in the lung and heart as well as in the systemic and the peripheral vasculatures. These responses are due to both neural reflexes and the activation of humoral receptors by circulating mediators (1). Histamine, a major mediator released by IgE activation, participates in many of the immediate cardiopulmonary physiologic consequences of inhaled antigen in both humans (2) and dogs (3). Histamine is released from mast cells and basophils in the alveolar interstitium and in bronchial mucosa. The number of mast cells in the alveoli (350/mm²) (4) markedly exceeds that in the bronchial mucosa, 226/mm² (5) when the relative surface areas of each are considered. Histamine can activate pulmonary C fibers (6), bronchial C fibers (7), and bronchial irritant fibers (8,9). The stimulation of select subsets of each of these fibers has been shown to increase bronchopulmonary smooth muscle tone (9) and elicit the pulmonary chemoreflex typified by rapid shallow breathing, bradycardia, and hypotension. Histamine (10) and inhaled allergens (11) stimulate mucociliary transport. As the functions of the respiratory central pattern generator, bronchial and vascular smooth muscle, and the mucosa are quite distinct, the relative responses of and pathways through which each of these responds to histamine and allergens must each be evaluated.

To determine the relative cardiovascular, respiratory, and epithelial responses elicited by histamine administered to the alveolar, bronchial, and vascular compartments and the role of neural pathways in mediating these events, we conducted a series of experiments in beagle dogs. In addition we evaluated cardiovascular, respiratory, and epithelial responses elicited by ragweed allergen administered to the alveolar and bronchial compartments in a cohort of ragweed-sensitized dogs and nonsensitized siblings. Activation of the pulmonary chemoreflex was demonstrated by the measurements of respiratory rate, heart rate, and arterial blood pressure. Efferent responses of the mucosa were assayed in terms of mucociliary clearance, whereas responses of smooth muscles were indicated by either pulmonary resistance or transpulmonary pressure and compliance. Indication of histamine or allergen-induced impairment of gas exchange was determined from the measurement of minute ventilation and arterial blood gases. In these experiments, equivalent total masses of histamine (approximately 185 µg) deposited in the lungs were partitioned such that in one set of experiments 71% was deposited in the bronchi; in the other set 91% was deposited in the alveoli. Responses from the predominantly alveolar deposition due to the 9% deposited in the bronchi were assessed separately by depositing 16 µg in the bronchi. The contribution of vagal transmission was

ascertained following bilateral sectioning of the vagosympathetic trunks. To evaluate the extent to which histamine-induced responses due to its translocation from the airways to the blood were transmitted via the central nervous system (12) or from direct cardiovascular regulation, we administered 200 µg of histamine intravenously (iv) to dogs with and without bilateral vagotomy. To evaluate the extent to which the histamine-induced responses could be attenuated by an anti-asthma agent that stabilizes cell membranes and, similar to cromolyn sodium (13) likely desensitizes sensory nerves, we administered nedocromil before administering histamine. In the experiments in which ragweed was administered, 0.4–1.8 µg ragweed were deposited in the lungs. During bronchial deposition 37% was deposited in the bronchi and during alveolar deposition 90% was deposited in the alveoli (11).

Methods

Experimental procedures were approved by the Animal Care Committee at the University of Illinois at Chicago. The beagle dogs were either obtained from the Chicago School of Medicine (North Chicago, IL, USA) or Veterans Affairs (Westside Division, Chicago, IL, USA) or bred at the University of Chicago (Chicago, IL, USA). They were conditioned and housed in a controlled environment at the University of Illinois at Chicago, which is approved by the American Association for Accreditation of Laboratory Animal Care. Studies were separated by intervals of at least 1 week. Experiments on histamine were conducted on 10 adult beagle dogs (3 females, 7 males) weighing 11.0 ± 0.4 kg. Cardiac responses are reported for 5 of 7 dogs sensitized to ragweed

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allergen. These data are derived from the raw data of a study previously published (11).

Delivery of Aerosols to the Bronchi and Alveoli

Two aerosol delivery systems were developed to deposit aerosols selectively in the lower respiratory tract of anesthetized beagles. One system delivered aerosols predominantly in the bronchial airways; the other delivered aerosols predominantly in the alveolar lung regions. At the time of an aerosol challenge, the dog's endotracheal tube was connected to either system. In the histamine study, both systems delivered aerosols created by an ultrasonic nebulizer (Microstat, Mountain Medical Equipment, Inc., Littleton, CO, USA), whereas in the allergen study, predominant bronchial deposition was obtained using a Fisoneb (Fisons Corp., Rochester, NY, USA) (mass median diameter of 5.5 μm). The systems were grounded to minimize aerosol loss due to electrostatic charge. Volume-controlled logic and timing circuitry was used to activate a sequence of solenoid valves (Automatic Switch Co., Florham Park, NJ, USA) to effect the desired aerosol delivery while maintaining adequate ventilation. In the histamine bronchial delivery system, the nebulizer was modified by removing the "fins," deflector baffle, and the valve; an additional tube was inserted between the nebulizer and the mouthpiece tube. A warmed humidifier placed at the input provided a source of moisture for particle growth. The tubing enroute to the nebulizer was warmed to prevent condensation. For deposition of aerosols predominantly into the bronchial lung region, the bronchial deposition system was set to deliver a 200- to 210-mL aerosol bolus 20 times per min at 60 L/min. Inhalation time was 0.2 sec and exhalation time was 2 sec followed by a 0.8-sec delay. In the alveolar aerosol delivery system, the only modification to the nebulizer was the removal of the one-way valve. Dry air from the compressed air source was not humidified. The aerosol delivery tubing was warmed to prevent aerosol growth by condensation. For deposition of aerosols predominantly into the alveolar regions, the system was set to deliver a 160-mL aerosol bolus followed by a 160- to 165-mL air bolus at 13–20 L/min at a rate of about 7 times per minute. Inhalation time was 1 sec, followed by a 5-sec breath hold; exhalation time was 2 sec followed by a 1-sec delay. Volume outputs were calibrated with a Collins respirometer (Collins, Braintree, MA, USA).

Dosimetry of Histamine and Nedocromil Aerosols Deposited in the Bronchi and Alveoli

Before conducting the physiologic protocols, the radioaerosol particulate tracer distribution within the aerosol according to particle size

and attenuation of activity in the dog's lungs was determined. The particle size generated by the nebulizer as provided by the manufacturer (without the valve) was measured at a flow rate of 28 L/min. The nebulizer was loaded with 2.5 mL of a 2-mg/mL fluorescein solution and 2.5 mL of a $\text{Tc}^{99\text{m}}$ sulfur colloid solution; particle size was determined using a cascade impactor (Andersen IACFM Mark II; Andersen Samplers, Inc., Atlanta, GA, USA). The mass median diameter \pm the geometric standard deviation was 1.7 $\mu\text{m} \pm 1.6$ based on the absorbance of fluorescein and 1.6 $\mu\text{m} \pm 1.4$ based on the counting of $\text{Tc}^{99\text{m}}$ activity. Nebulizer output consistency was checked periodically by collecting a fluorescein sodium (Sigma, St. Louis, MO, USA) aerosol on a filter, redissolving the particles into saline, and running a spectrophotometric assay for fluorescein. The counting efficiency of the gamma camera (Siemens, Chicago, IL, USA) to radioactivity deposited in the dog's lungs was determined by iv injection of a known amount of $\text{Tc}^{99\text{m}}$ -labeled albumin aggregate (Medi-Physics, Richmond, CA, USA) in an anesthetized dog. With this technique (13) the macroaggregates were assumed to lodge within the capillaries of the lung. Radioisotope calibration was performed with a radioisotope calibrator (model CRC-7; Capintec Inc., Ramsey, NJ, USA).

The mass of aerosol deposited per breath in the bronchi and alveoli was measured for both the bronchial and alveolar aerosol delivery systems for each of the 10 dogs in the histamine study and 7 dogs in the ragweed study. The fasted dog was anesthetized, restrained in the supine position on the gamma camera, and intubated. A radioaerosol consisting of $\text{Tc}^{99\text{m}}$ -labeled sulfur colloid (Medi-Physics, Inc.) was delivered to the lung using the bronchial or alveolar delivery systems. The animal was extubated prior to counting the

radioactivity in the lung. Scintigrams (Figure 1) revealed the separation of radioactivity in the bronchial and alveolar regions of the lungs. The radioactivity measured in the lungs was corrected for background activity and radioactive decay. This retention of activity represented total deposition in the lung. The retention of radioactivity measured in the lungs 24 hr after radioaerosol inhalation (following subtraction of background and correction for radioactive decay) was taken to represent the mass of aerosol deposited in the alveoli (14). This is based on the assumption that particles deposited in the bronchi are removed by mucociliary activity within 24 hr. The activity remaining after subtraction of the alveolar deposition from the total deposition represents bronchial deposition (1). The following volumes were calculated from the specific activity in the nebulizer. In the histamine study, the bronchial system delivered per breath to the lungs volumes of 0.7 μL , of which 0.5 μL was deposited in the bronchi and 0.2 μL in the alveoli; the alveolar system delivered a total lung volume of 2.3 μL , of which 0.2 μL was deposited in the bronchi and 2.1 μL in the alveoli. The masses of histamine and nedocromil deposited in each of the protocols (Table 1) were calculated from these volumes for both the bronchial and alveolar delivery systems. In the allergen study, in the bronchial mode, 34 μ (SE: $n = 7$) was deposited in 20 breaths, 37% of which was deposited in the bronchi; in the alveolar mode, 40 μ per 10 breaths was deposited, 90% of which was deposited in the alveoli.

Assays

Pulmonary Mechanics

In the histamine study, transpulmonary pressure (P_{tp}) and air flow (F) signals from the differential pressure transducers (model

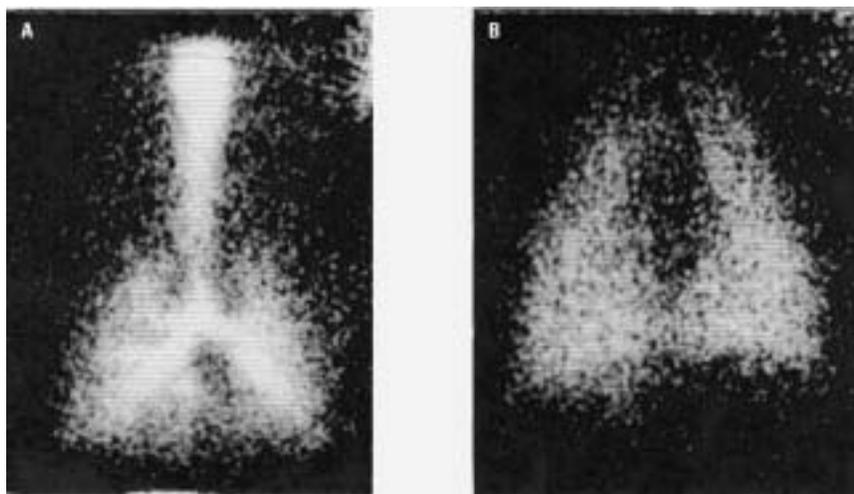


Figure 1. Scintigrams taken after predominantly bronchial (A) and alveolar (B) radioaerosol depositions.

MP45-28-871, 50 cmH₂O; model MP45-1-871 2 cmH₂O, respectively; Validyne Engineering Corp., Northridge, CA, USA) were amplified by a Buxco Preamplifier Bank and analyzed by an analog Buxco pulmonary mechanics analyzer (model 6; Buxco Electronics, Inc., Sharon, CT, USA). The isovolumetric reference algorithm (Program 1) of the Buxco pulmonary mechanics analyzer was used to derive tidal volume (V_T), respiratory rate (RR), minute volume (MV), lung resistance (R_L), and dynamic compliance (C_{dyn}). The derived P_{tp} , F, V_T , RR, MV, R_L , and C_{dyn} signals from the Buxco pulmonary mechanics analyzer were simultaneously sampled at a rate of 10 Hz/channel using an A/D converter board (model 2905; Data Translations, Marlboro, MA, USA) installed in a 386-16 computer, IBM-80 (IBM, Armonk, NY, USA) and stored permanently on diskettes for later off-line, breath-by-breath analysis on an IBM 4340 mainframe. This system was calibrated using a volumetric syringe for volume, a water manometer for pressure, and with an internal calibration procedure provided within the Buxco. In the ragweed study a similar but updated system was used (11).

Tracheal Ciliary Beat Frequency

In the histamine study, tracheal ciliary beat frequency (CBF_t) was measured using a non-stationary heterodyne laser light-scattering system (15). Briefly, an He-Ne laser beam was transmitted down the axis of a hollow stainless steel probe (30 cm long, 4.5 mm ID and 8 mm OD). The beam exited perpendicularly from the probe and was focused on a 7- μ m focal spot coincident with the surface of the ciliated epithelium 5 mm from the probe surface. The predominant frequency of the signals resulting from the scattered photons derived from a time-frequency bilinear distribution was defined as CBF_t. CBF_t was calculated approximately every 3.5–5 sec. The system was calibrated using a stroboscope.

Protocols

Animal Preparation for Challenges

Histamine study. Before each experiment, dogs were fasted for 12 hr but allowed access to water. Each dog was anesthetized with 2.5% thiamylal sodium iv to effect (loss of palpebral and toe-pinch reflexes), restrained in a supine position, and intubated with a size 7 Hi-Lo Jet (Mallinckrodt, Inc., St. Louis, MO, USA) endotracheal tube (in one dog, a size 6 endotracheal tube was used). The cuff of the endotracheal tube was inflated in the distal trachea. Supplemental doses of thiamylal sodium were given throughout the study as needed to minimize palpebral and toe-pinch reflexes. A catheterized esophageal balloon (1.5 \times 10 cm) was fed through the esophagus and connected to a 50 cmH₂O differential pressure transducer (model MP45-28-871; Validyne Engineering Corp.). The other port of the pressure transducer was connected to the largest side port of the endotracheal tube. This differential pressure represented P_{tp} . The probe for measuring ciliary beat frequency was carefully inserted on the ventral side of the tracheal lumen such that the laser beam focal spot coincided with the lateral wall of the mid-trachea. The proximal end of the endotracheal tube was connected to a heated (37°C) pneumotach (model 3700, 0–160 L/min, Hans Rudolph, Inc., Kansas City, MO, USA) coupled to a 2 cmH₂O differential pressure transducer (model MP45-1-871, Validyne Engineering Corp.) to measure flow rate. The femoral artery was cannulated to both monitor arterial blood pressure (BP) (model P23ID; Gould Statham Instruments Inc., Cleveland, OH, USA) and to sample blood for blood chemistry measurements (model 1312 BGM; Instrumentation Laboratory, Inc., Lexington, MA, USA). Heart rate, partial pressure of oxygen in blood (SpO₂) (pulse oximetry finger probe clamped to tongue), end-tidal CO₂ (carbon dioxide), respiratory rate (model ULT-S-27-00; Datex, Tewksbury, MA, USA), electrocardiogram

(model EK/5A; Burdick Corp.; model 78312A; Hewlett Packard, Waltham, MA, USA), and rectal temperature (model 5800; Omega Engineering, Inc., Stamford, CT, USA) were monitored continuously. Arterial BP and the pulmonary mechanics parameters previously described were recorded on the 6-channel chart recorder (model 2600; Gould, Inc., Cleveland, OH, USA).

Bronchial and Alveolar Histamine Inhalation Challenges

The experimental design is described in detail in Table 1. Studies *a–i* were performed in separate experiments for each dog. Each dog was allowed at least 1 week recuperation between experiments. Eight experiments (studies *a* and *c–i*) were performed in each of 10 anesthetized dogs using a randomized block design. Following these studies, a bronchial vehicle challenge (study *b*) was added and performed randomly in 8 of 10 dogs. As described in the table, the experiments consisted of a control study using the alveolar delivery system to deliver the vehicle phosphate-buffered saline (PBS), pH 7.4, predominantly to the alveolar region of the lung (study *a*); a control study using the bronchial delivery system to deliver the vehicle predominantly to the bronchial region of the lung (study *b*); histamine delivery at a low dose using the bronchial delivery system to deliver predominantly to the bronchial region of the lung (study *c*); histamine delivery at a high dose using the alveolar delivery system to deliver predominantly to the alveolar region of the lung, keeping the bronchial dose the same as in study *c* (study *d*); and histamine delivery at a high dose using the bronchial delivery system to deliver predominantly to the bronchial region of the lung, keeping the total mass the same as in study *d* (study *e*). These five studies also included a vehicle pretreatment challenge with 0.9% saline using the alveolar delivery system. These pretreatments were control deliveries for studies *f–h* in which nedocromil sodium (Fisons Corp.) dissolved in 0.9% saline was delivered as the pretreatment agent. The effect of nedocromil pretreatment on the alveolar histamine-induced changes in the physiologic parameters measured were investigated in studies *f–i*. Following a 20-min stabilization period, data collection commenced. Baseline data were collected for 15 min before aerosol pretreatment with 0.9% saline or 0.01, 0.1, 1.0 mg/mL (alveolar delivery) or 0.4 mg/mL (bronchial delivery) nedocromil in 0.9% saline. Fifteen minutes later either PBS or 8 mg/mL histamine diphosphate (ICN Biochemicals, Cleveland, OH, USA) in PBS was aerosolized and data were acquired for 90 min. Blood chemistry values were recorded during the baseline phase, the pretreatment phase, and at 5, 10, 60, and 90 min during the treatment phase.

Table 1. Experimental study design.

Study	Pretreatment		Treatment		Agent	Dose (μ g)		
	Agent	Site	Agent	Site		B	A	T
a	sal (5) ^a	A	PBS (10) ^a	A	his	0	0	0
b	sal (5)	A	PBS (33)	B	his	0	0	0
c	sal (5)	A	his (4)	B	his	16	6	22
d	sal (5)	A	his (10)	A	his	16	168	184
e	sal (5)	A	his (33)	B	his	132	53	185
f	ned (5)	A	his (10)	A	ned	0.01	0.1	0.11
			his (10)	A	his	16	168	184
g	ned (5)	A	his (10)	A	ned	0.1	1.0	1.1
			his (10)	A	his	16	168	184
h	ned (5)	A	his (10)	A	ned	1.0	10.0	11.0
			his (10)	A	his	16	168	184
i	ned (5)	B	his (10)	A	ned	1.0	0.4	1.4
			his (10)	A	his	16	168	184

Abbreviations: A, alveolar dose; B, bronchial dose; his, histamine; ned, nedocromil; sal, 0.9% saline; T, total dose. ^aNumbers in parentheses refer to the number of breaths.

Each of these separate experiments (*a-f*) lasted approximately 2.5–4 hr. Of the 88 studies performed, pulmonary data from 1 dog in study *b* and 1 dog in study *g* were excluded from the analysis because of problems with the data acquisition program.

Intravenous Histamine Challenge

To determine the contribution to the cardiopulmonary responses due to histamine in the blood, 200 μg of histamine in PBS were administered iv to 8 of 10 dogs in a tenth study. These experiments were performed in anesthetized beagles following completion of all the histamine inhalation challenge studies. After a 20-min stabilization period, baseline data were collected for 15 min, followed by iv histamine injection. The duration of the injection was 1.5 min (to approximate the histamine aerosol inhalation time). During the histamine injection, a sham challenge consisting of 10 breaths of 0.9% saline aerosol was delivered to the alveolar region using the alveolar delivery system. Subsequent measurements of CBF_t and ventilatory and pulmonary function parameters were collected for 1 hr in 8 dogs, followed by iv PBS injection with a sham inhalation challenge and another 15 min of data collected from 7 of 8 dogs. Blood chemistry data were recorded 5 min before and 5, 10, and 60 min after the iv histamine challenge, and 5 and 10 min after the iv PBS challenge. Each experiment lasted 2–3.5 hr.

Histamine Challenges Following Vagotomy

The vagal contributions to the effects of histamine observed in studies *d* and *e* and in the iv histamine study were assessed by performing a bilateral cervical vagotomy in a terminal study in 8 of 10 dogs. Following anesthesia and a 20-min stabilization period, 15 min of baseline data were collected. The vagosympathetic trunks were exposed and data collected for 15 min (prevagotomy period). The right and left vagus nerves were cut simultaneously and data collected for 15 min (postvagotomy period). Next, histamine (200 μg) was injected iv followed by a 30-min data collection period. Following this, 10 breaths of histamine were delivered by the alveolar delivery system and 30 min of data collected. The last challenge in sequence consisted of 33 breaths of histamine delivered by the bronchial delivery system and 1 hr of data collection. Blood chemistry data were recorded at 10 min during the baseline, prevagotomy, and postvagotomy period; 5 and 10 min after iv histamine; 5 and 10 min after the alveolar histamine challenge; and 5, 10, and 60 min after the bronchial histamine challenge. Each experiment lasted 4–6 hr.

Ragweed studies. The animal preparation and protocols have been described previously in detail (11). The animal preparation and protocols were similar to those in which histamine was targeted primarily to the bronchial

and alveolar regions of the lungs but with the anesthetic being a combination of propofol and etomidate.

Statistics

All data are presented as the mean \pm SE unless noted otherwise. The Wilcoxon signed rank test was used to test for differences between treatments for nonparametric data. If the data were normally distributed, the paired t-test was used. One-tailed significance was assigned at $p < 0.05$.

Results

Bronchial and Alveolar Deposition Patterns

Scintigrams as those in Figure 1A and 1B show the deposition patterns from bronchial and alveolar depositions. Such patterns were seen in both the histamine and ragweed studies.

Cardiovascular and Respiratory Responses to Histamine

The mean temporal changes in respiration and pulmonary mechanics due to low-dose bronchial histamine, high-dose alveolar histamine, and high-dose bronchial histamine are shown in Figure 2A, 2B, and 2C, respectively. The low bronchial dose of histamine did not cause any significant change in the mean pulmonary mechanics parameters when compared to mean control values of all dogs

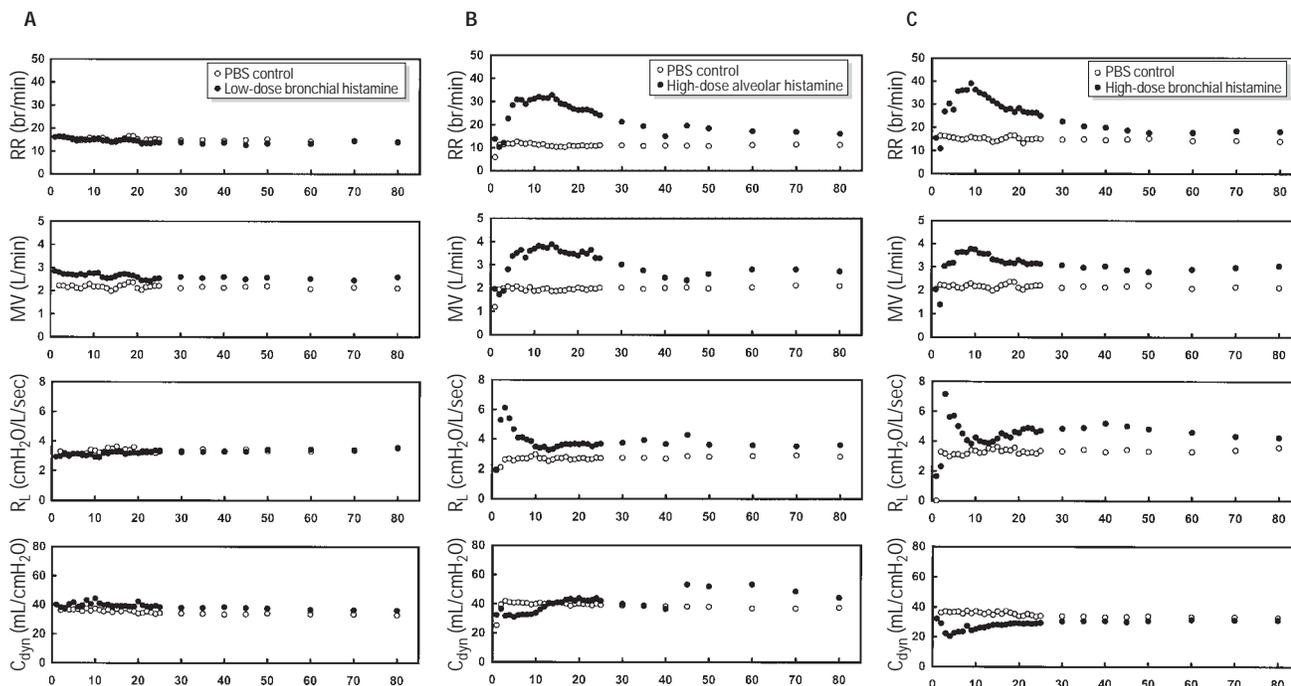


Figure 2. Temporal pulmonary mechanics data after PBS control aerosols ($n = 7$ for bronchial control and $n = 10$ for alveolar control) and histamine aerosols for the (A) low bronchial histamine challenge ($n = 10$), (B) high alveolar histamine challenge ($n = 10$), (C) and high bronchial histamine challenge ($n = 10$). Data were averaged over 1-min periods beginning with 0–1 min through 25–26 min, followed by 5- and then 10-min averages for each dog study. Each datum point represents the mean of the averaged data for all dogs. Vehicle or histamine inhalation begins at 1 min.

(Figure 2A), although there appeared to be a small increase in MV not related to an increase in RR. Any changes in these parameters observed during the high alveolar challenge must therefore be the result specifically of alveolar-induced changes. There was no appreciable effect of the low bronchial dose of histamine on partial pressure of CO₂ in arterial blood (P_{CO₂}) at any time point.

The maximal mean histamine-induced changes in respiration, pulmonary mechanics, heart rate, and BP for the alveolar deposition, bronchial deposition and iv administration for similar total doses of histamine are shown in Table 2. Bronchial and alveolar deposition of histamine caused apneas of 58 ± 11 sec and 56 ± 9 sec, respectively. No apnea was observed during the iv delivery of histamine. RR doubled and MV increased 1.7 times 6–7 min following alveolar and bronchial histamine, whereas there were no significant increases in these parameters following iv administration of histamine. R_L increased by more than a factor of 2 following both alveolar and bronchial histamine, although the increase following bronchial histamine did not reach statistical significance (*p* < 0.07). These increases in R_L were maximal at 3 min posthistamine administration for all routes of administration and returned to control values within 9–10 min. Minimal changes were observed in RR and MV following iv histamine administration. Following either bronchial or alveolar histamine, substantial decreases in C_{dyn} occurred between 3 and 10 min, with the bronchial histamine causing a greater decrease in C_{dyn} in 9 of 10 dogs. Again, any changes in pulmonary mechanics following iv histamine were minimal. Following alveolar histamine there were secondary increases in R_L and decreases in C_{dyn} at 45 min as well as a concurrent increase in RR (Figure 2B). There was also a secondary increase in R_L 40 min after the bronchial histamine challenge (Figure 2C). These secondary responses were not observed following iv histamine. Changes in heart rate due to alveolar histamine were unremarkable. Small decreases in heart rate were observed immediately

following bronchial histamine. The decreases in systolic BP were significant for all treatments but were most dramatic following iv histamine. The high alveolar histamine dose caused a small increase in P_{CO₂} at 5 min; it returned to a near-baseline level by 10 min. The high bronchial histamine dose caused a greater increase in P_{CO₂} at 5 min than the high alveolar histamine dose and, unlike with the high alveolar histamine dose, P_{CO₂} did not return to near baseline levels until some time after the 10-min reading. The changes in partial pressure of O₂ in arterial blood (P_{O₂}) reflected the changes in P_{CO₂}. Intravenous administration of histamine did not appreciably affect P_{CO₂} or P_{O₂} at any time. In these experiments, any effects of histamine on CBF_t were not evident. Also, nedocromil pretreatment did not affect CBF_t.

Effects of Nedocromil on Histamine-Induced Pulmonary and Vascular Responses

Nedocromil administration to the alveolar and bronchial regions of the lung at all doses attenuated the RR and MV responses to alveolar histamine beginning at 4–5 min. Initially this appeared to be independent of dose but was more clearly dose dependent at 20 min. Nedocromil abolished the second rise in C_{dyn} occurring at 40–45 min (data not shown). At 20 min, RR with histamine alone was 26 ± 8 breaths (br)/min and after alveolar nedocromil pretreatments of 0.1, 1, and 10 µg was 20 ± 8, 16 ± 4, and 14 ± 3 br/min, respectively. Similarly, following bronchial deposition of 1 µg of nedocromil, RR was 14 ± 2 br/min. At 20 min, MV with histamine alone was 3.4 ± 0.8 L/min and after each alveolar pretreatment with nedocromil was 2.8 ± 0.6, 2.3 ± 0.3, and 1.8 ± 0.2 L/min, respectively. Similarly, following bronchial pretreatment with 1 µg of nedocromil, MV was 2.2 ± 0.2 L/min. Surprisingly, the lowest alveolar nedocromil dose decreased the peak R_L response the most. Peak R_L decreased from 6.4 ± 1.1 cmH₂O L/sec to 4.9 ± 0.6, 5.4 ± 0.6, and 6.1 ± 1.0 cmH₂O L/sec, respectively. There was no attenuation of the

histamine-induced increases in R_L due to bronchial deposition of nedocromil. In this case R_L was 7.0 ± 1.7 cmH₂O L/sec. Not only did nedocromil not prevent the decreases in C_{dyn} induced by histamine, the return to control levels was delayed approximately 20 min at all doses of nedocromil independent of its site of deposition. Prior deposition of nedocromil to the alveolar region at either the lowest or highest concentrations did not affect the decrease in systolic blood pressure caused by the high alveolar histamine challenge, 39 ± 4 versus 34 ± 4 mmHg (*p* = 0.37), and 31 ± 5 versus 34 ± 4 mmHg (*p* = 0.425), respectively.

The effects on P_{CO₂} and P_{O₂} due to alveolar histamine following pretreatment with nedocromil are shown in Figure 3A and 3B, respectively. When the dogs were pretreated with nedocromil, the increases in P_{CO₂} due to histamine delivery to the alveoli were ameliorated in a dose-dependent manner. Not surprisingly, nedocromil delivered to the alveolar region was more effective in attenuating the increase in P_{CO₂} due to alveolar histamine than the same dose of nedocromil (1 µg deposited) delivered to the bronchi. The effects of histamine with nedocromil on P_{O₂} values were physiologically consistent with the changes in P_{CO₂}.

Effects of Vagotomy on the Histamine-Induced Respiratory and Cardiac Responses

The influence of bilateral transection of the cervical vagosympathetic trunk on the temporal respiratory responses initiated by iv histamine, high-dose alveolar histamine aerosol, and high-dose bronchial histamine aerosol can be summarized as follows. The ventilatory responses to histamine were abolished after cutting the vagosympathetic trunks, as demonstrated by the abolition of the increases in RR. The R_L at 3 min increased from 5.0 ± 0.5 cmH₂O L/sec (postvagotomy) to 6.5 ± 0.8 cmH₂O L/sec after iv histamine, 7.6 ± 1.9 cmH₂O L/sec after alveolar histamine delivery, and 8.9 ± 1.9 cmH₂O L/sec after bronchial histamine delivery. R_L values returned to near-post-transection baseline values by 6 min after iv histamine and by 9 min after alveolar histamine, whereas after bronchial histamine R_L did not return to baseline level throughout the duration of the study. Sectioning of the vagosympathetic trunks abolished the histamine-induced decreases in C_{dyn}.

As the vagotomy, per se, changed the baseline respiratory parameters, i.e., decreased RR and increased V_T, peak changes from baseline for RR, R_L, and C_{dyn} were compared to peak changes when the vagosympathetic trunks were intact. It can be seen in Figure 4A that sectioning the vagosympathetic

Table 2. Respiratory and cardiovascular peak responses.^a

	High alveolar		High bronchial		Intravenous	
	Control	Histamine	Control	Histamine	Control	Histamine
RR (br/min)	13 ± 2	31 ± 9*	15 ± 2	36 ± 9 (NS)	15 ± 2	19 ± 5 (NS)
MV (L/min)	2.1 ± 0.1	3.5 ± 0.6*	2.1 ± 0.2	3.6 ± 0.6*	2.4 ± 0.2	2.9 ± 0.3 (NS)
R _L (cmH ₂ O/sec)	2.6 ± 0.3	6.1 ± 1.1**	3.2 ± 0.6	7.2 ± 1.6 (NS)	3.4 ± 0.4	3.9 ± 0.5 (NS)
C _{dyn} (mL/cmH ₂ O)	41.9 ± 2.4	31.5 ± 4.4*	37.0 ± 4.0	22.2 ± 6.1**	31.9 ± 4.1	24.4 ± 4.3 (NS)
HR (beats/min)	114 ± 10	115 ± 10 (NS)	127 ± 22	116 ± 9*	120 ± 12	112 ± 8 (NS)
BP (mmHg)	177 ± 9	144 ± 8***	180 ± 14	152 ± 14**	180 ± 7	109 ± 10***
P _{CO₂} (mmHg)	41.9 ± 1.3	46.0 ± 2.3*	41.6 ± 1.6	48.8 ± 2.2**	48.8 ± 0.9	48.6 ± 1.8 (NS)
P _{O₂} (mmHg)	93.0 ± 3.4	74.4 ± 7.3*	94.6 ± 2.3	56.0 ± 7.1**	93.6 ± 2.7	87.5 ± 6.6 (NS)

NS, not significant.

^aHistamine P_{CO₂} and P_{O₂} are from the 5-min posthistamine blood samples. **p* ≤ 0.05; ***p* ≤ 0.005; ****p* ≤ 0.00005.

trunks totally abrogated any increases in RR induced by iv, alveolar, and bronchial delivery of histamine. The effects of vagotomy on histamine-induced increases in R_L tell a different story (Figure 4B). Small changes in R_L induced by iv histamine did not appear to be attenuated by transection of the vagosympathetic trunks. The average changes in R_L induced by iv histamine when the vagi were intact compared to when they were sectioned were not significant (1.2 ± 0.3 vs 1.7 ± 0.6 $\text{cmH}_2\text{O L/sec}$). The differences in R_L after bronchial and alveolar histamine challenges following vagosympathetic trunk transection are best illustrated by contrasting the patterns of response in Figure 4B. It can be seen that

sectioning the vagosympathetic trunks followed by the alveolar histamine challenge decreased R_L in 6 of 8 dogs. There was a noted exception in one dog; however, these changes were not statistically significant. When histamine was deposited primarily in the bronchial regions, the change in R_L increased in 5 of 8 dogs; in 3 dogs it was markedly augmented. However, there was no significance in the mean change. The mean change in R_L after the alveolar histamine challenge was 3.7 ± 1.2 $\text{cmH}_2\text{O L/sec}$ (intact) versus 3.5 ± 2.2 $\text{cmH}_2\text{O L/sec}$ (postvagotomy) and 4.7 ± 1.1 $\text{cmH}_2\text{O L/sec}$ (intact) versus 6.5 ± 2.0 $\text{cmH}_2\text{O L/sec}$ (postvagotomy) for the bronchial histamine challenge.

Bilateral sectioning of the vagosympathetic trunks attenuated the histamine-induced increases in C_{dyn} whether histamine was administered iv or predominantly to the bronchi or alveoli ($p < 0.05$) (Figure 4C).

The heart rate increased only slightly following transection of the vagosympathetic trunks (103 ± 9 vs 107 ± 10 beats/min, $p = 0.13$). There were nonsignificant changes in heart rate after iv histamine (107 ± 10 vs 97 ± 11 beats/min, $p = 0.13$), alveolar histamine (107 ± 10 vs 121 ± 12 beats/min, $p < 0.11$), and bronchial histamine (107 ± 10 vs 111 ± 12 beats/min, $p = 0.44$) when the vagosympathetic trunks were cut. Mean systolic BP was not significantly increased following transection of the vagosympathetic trunks (170 ± 5 vs 175 ± 8 cmH_2O , $p = 0.16$). The immediate response of systolic BP to iv, alveolar, and bronchial histamine was in the same rank order and of similar magnitude whether the vagosympathetic trunks were intact, suggesting only a minor role for vagosympathetic transmission in the histamine-induced decreases in BP.

During the studies in which the vagosympathetic trunks were cut, iv histamine caused an increase in P_{CO_2} from 43.5 ± 1.8 to 46.4 2.8 mmHg after 5 min and to 50.1 ± 3.2 mmHg after 10 min. The corresponding changes in P_{O_2} were from 89.0 ± 4.1 to 78 ± 6.0 and 66.5 ± 8.2 , respectively. Alveolar histamine caused the P_{CO_2} to increase to 48.3 ± 1.8 mmHg at 5 min, which dropped to 47.3 ± 2.1 mmHg at 10 min. The corresponding changes in P_{O_2} were 71.8 ± 5.9 mmHg and 76 ± 6.2 mmHg, respectively. Bronchial histamine caused the P_{CO_2} to increase to 49.0 ± 2.9 mmHg at 5 min and to 48.4 ± 2.9 mmHg at 10 min and decrease to a near baseline value of 46.4 ± 2.2 mmHg at 60 min. The corresponding changes in P_{O_2} were from 72.7 ± 8.3 , 75.9 ± 8.0 , and 76.8 ± 8.8 mmHg, respectively. The effects of histamine challenges on P_{O_2} were consistent with the effects observed for P_{CO_2} . Sectioning of the vagosympathetic trunks and histamine challenges post-transection did not have an effect on CBF_i at any time.

Cardiovascular Responses to Bronchial and Alveolar Depositions of Ragweed in Ragweed-Sensitized Dogs

The cardiac and vascular responses to alveolar ragweed are shown in Figure 5A. There was a marked decrease in both heart rate and BP that were maximal after 1 min following the end of alveolar ragweed inhalation. The decreases in BP due to allergen inhalation were evident in the measurements of both systolic and diastolic pressures. Even though the time of delivery of histamine and ragweed were similar, the marked precipitous fall in heart rate observed after alveolar allergen

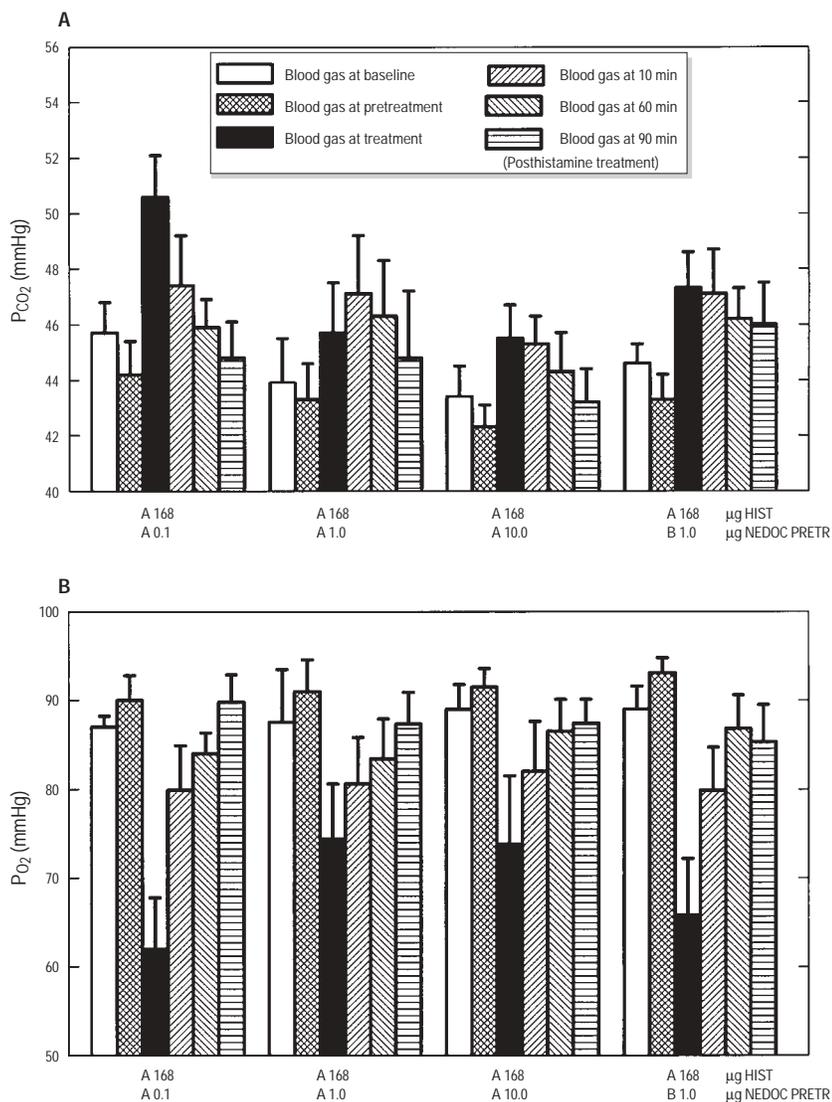


Figure 3. (A) Mean P_{CO_2} values recorded for studies *f-i*. In each study, the first bar represents the mean baseline value (20 min prior to challenge). The second bar is the mean pretreatment value (5 min prior to challenge). Bars 3–6 are the mean treatment values (5, 10, 60, and 90 min after the beginning of the challenge). The microgram doses of histamine (HIST) and nedocromil (NEDOC PRETR) for the bronchial (B) and alveolar depositions (A) are shown under the x-axis. (B) Mean P_{O_2} values for studies *f-i*.

inhalation was not observed after histamine inhalation, although both histamine and ragweed inhalation resulted in marked decreases in BP. In these 5 dogs, allergen challenge induced rapid shallow breathing, with the respiratory rate increasing from 11.2 to 134 br/min and the minute ventilation increasing from 1.5 L/min to 5.2 L/min. It is notable that the maximal changes in respiration and in the mechanical properties of the lungs occurred 10–14 min after the ragweed challenge (Figure 5B).

Discussion

Partitioning of aerosol deposition to the bronchial and alveolar lung regions was crucial to the investigation of site specific-initiated changes in cardiopulmonary function. The lack of responses observed in the experiments consisting of a low bronchial dose of histamine (16 μg) using the bronchial mode of deposition confirmed that the responses to high-dose alveolar histamine using the alveolar mode of deposition were due to the alveolar dose of histamine (168 μg) and not to the 16 μg deposited in the bronchial airways. The changes in lung function observed with histamine aerosols could not be attributed to circulating histamine because the same total dose of iv histamine was without substantial effect on lung parameters, and changes, if any, were transient. This minimal iv effect on pulmonary mechanics confirms that the observed respiratory responses were not caused by histamine acting centrally (10). Histamine released from mast cells is transferred to the blood with a half-time of 2.5 min (2), increasing about 750 times to 800 ng/mL (3). The roughly 200 ng/mL resulting from the 200- μg injection appears well within the physiologic range but higher than the 6.6 ng/mL measured by Chrusch et al. (10) following a ragweed-induced anaphylactic shock. Thus, these results are a novel set of experimental data in which the responses to documented alveolar, bronchial, and systemic histamine quantities can be compared to elucidate the physiologic effects of histamine at these doses and effector sites.

The doses of histamine deposited in the lungs in these studies (approximately 185 μg) produced more than a 200% increase in R_L . In a study by Wanner et al. (17), 110 μg produced a 10% decrease in forced expiratory volume in 1 sec (FEV_1) in healthy humans. Although they used somewhat different inhalation protocols, it was concluded that the bronchial responsiveness correlated with the mass of histamine deposited rather than with the deposition pattern. Our data, obtained from extreme deposition patterns resulting in markedly different concentrations of histamine in terms of location and surface area

distribution, concur with this conclusion. At variance with this are the results of Ruffin et al. (18), who reported that the dose of histamine sufficient to cause a 20% decrease in FEV_1 (PD_{20}) for central and diffuse deposition patterns were 6 and 34 μg of histamine deposited, respectively. The 200 μg we slowly administered iv gave minimal if any changes in R_L and contrasted with the 500, 5,000, and 50,000 μg boluses of histamine administered iv to paralyzed pentobarbital-anesthetized dogs (19). Using those high doses and that anesthetic regime, nonvagal mediated increases in bronchoconstriction could be anticipated (20–22).

Because all changes in RR (including any increase cause by iv histamine) were ablated by transection of the vagosympathetic trunk, it is clear that histamine-induced increases in RR were initiated in the lungs and mediated via afferents that traverse the vagosympathetic trunk. When the histamine deposition was predominantly bronchial, the increase in RR

was likely due to the stimulation of bronchial C fibers (8) or rapidly adapting sensory nerves (6,8). When the deposition was predominantly peripheral, the increase was likely due to alveolar C fibers, as these are the major determinants of irritant-induced increases in respiratory rate (6). Although pulmonary C fibers respond to inhaled histamine (6), they may not be as sensitive to inhaled histamine as bronchial C fibers (7). It appears from our studies described herein that the integrated response in the alveoli is similar to the integrated response from the bronchial C fibers and rapidly adapting sensory nerves. These increases in RR likely were initiated at first by activation of H_1 and H_2 receptors on sensory nerves, as antagonists to each of these receptors abolished the increase in RR due to inhaled micron-sized histamine aerosols, as shown in baboons (23). The RR responses peaked at a later time than the peak response in R_L and lasted longer than the increases in R_L . This is consistent with the notion that the

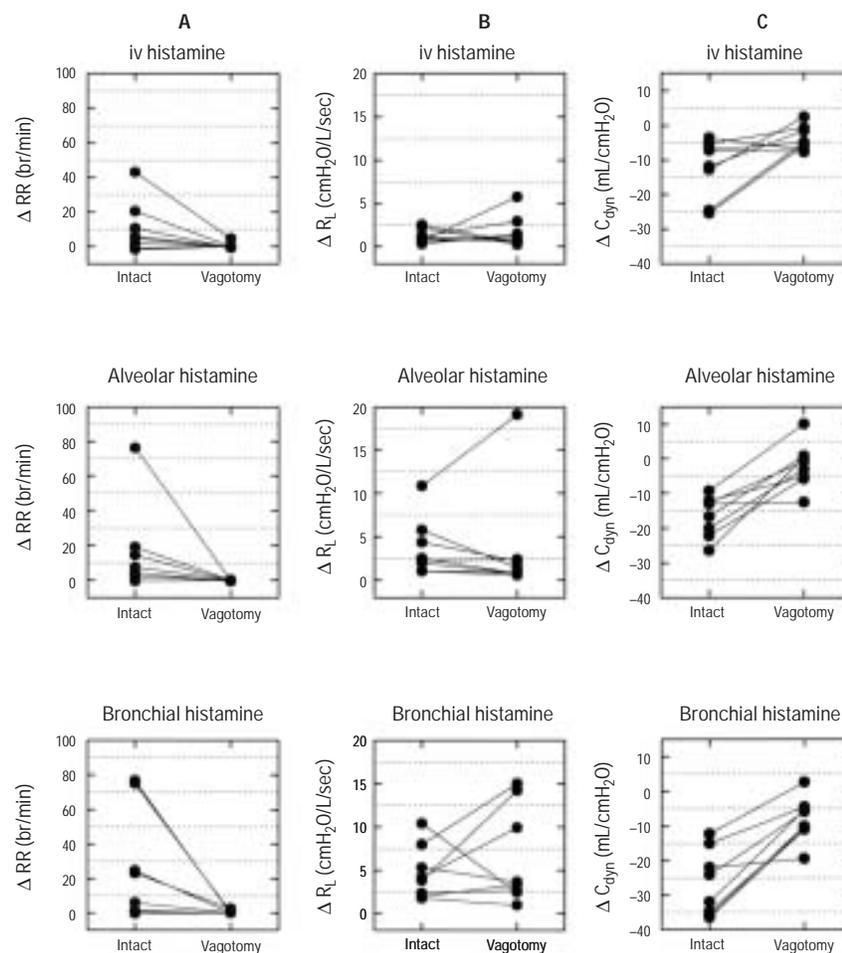


Figure 4. Effect of vagosympathetic trunk transection on the change in (A) respiratory rate, (B) lung resistance, and (C) dynamic compliance from baseline after iv high alveolar and high bronchial histamine challenges ($n = 8$). The mean baseline value for each dog (mean of the first 6 min of averaged data) was subtracted from the value post-challenge showing the greatest change (1-min averaged value occurring in less than 6 min).

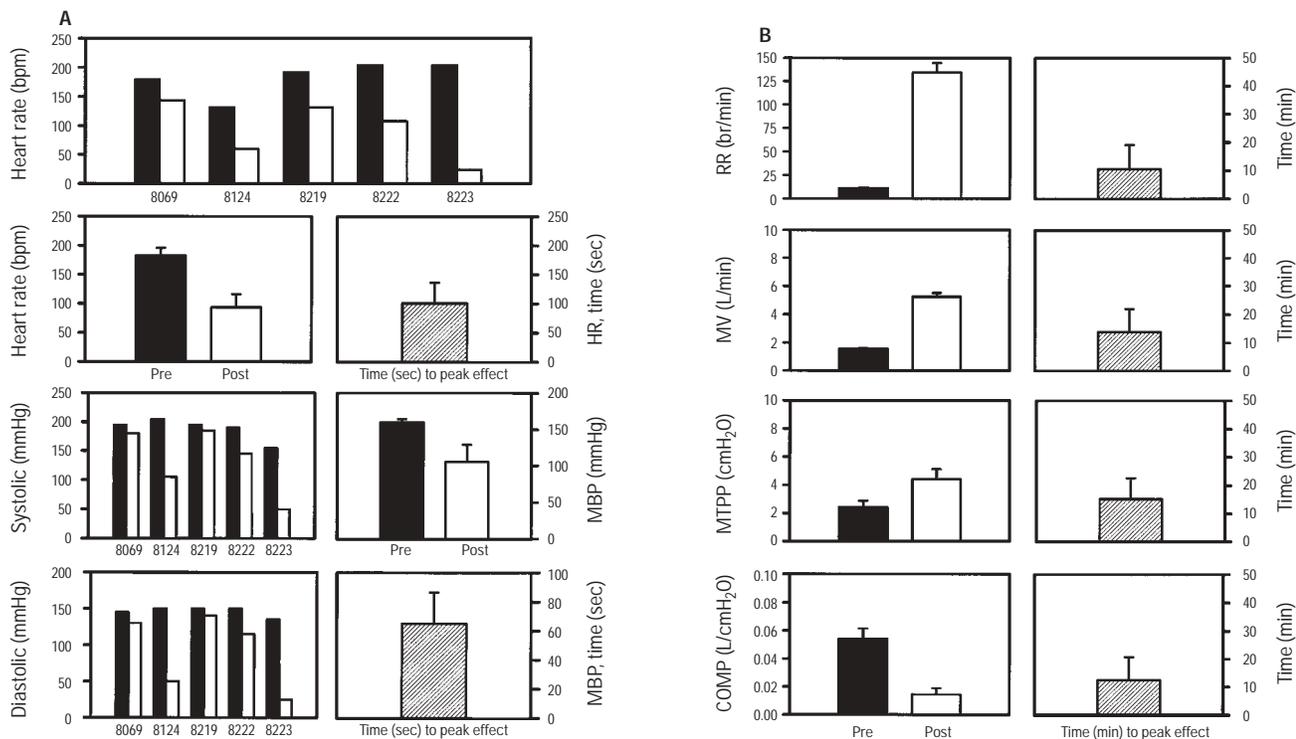


Figure 5. Times and magnitudes of the peak responses of (A) the cardiovascular system and (B) the respiratory system in an average of 5 dogs following the end of inhalation of microgram quantities of ragweed extract for 1–1.4 min using techniques that specifically targeted deposition in either the bronchial or alveolar regions of the lungs, respectively (17). bpm, beats per minute; COMP, dynamic compliance; MBP, mean blood pressure; MTPP, mean transpulmonary pressure. 8069, 8124, 8219, 8222, and 8223 indicate the dogs' numbers.

sensory nerves responsible for the regulation of respiratory rate are independent of those that regulate bronchomotor tone, although both C fibers and rapidly adapting sensory nerves may play a role in both responses (9).

The observations that the immediate marked decreases in BP were not due to commensurate decreases in heart rate, that these decreases were progressively larger when similar masses of histamine were administered predominantly to the bronchi, alveoli, and iv, and that these decreases were only slightly attenuated by transection of the vagosympathetic trunks indicate that the major portion of these histamine-induced decreases in BP were likely due to pulmonary vasoconstriction and systemic vasodilation, as previously reported in dogs (24); both effects were markedly ameliorated by combined H₁ and H₂ blockade.

Although in a similar canine model of ragweed-induced anaphylaxis an iv dose of 100–80,000 µg was required to produce the anaphylactic shock (16), only 0.4–1.8 µg of ragweed allergen was required for deposition by aerosol in the lungs (17). This 250- to 40,000-fold difference may be due to the direct delivery of the allergen to the primary target organ, the decrease in allergen sensitivity in pentobarbital-anesthetized compared to propofol/etomidate-anesthetized dogs, or some other factor. We have preliminary data

that suggest the anesthetic regime may play a major role.

The precipitous decrease in heart rate may be attributable to a neural reflex initiated in the lungs and or to the direct activation of cardiac mast cells (25) by antigen permeating into the blood; we consider the former more likely. The decreases in BP induced by ragweed challenge in the alveoli appeared to occur proportionately in both systolic and diastolic pressure. Although a decrease in left ventricular function as observed by Chrusch and colleagues (16) cannot be ruled out, it is likely that this decrease was caused by a decrease in heart rate and peripheral and systemic vasodilation together with an increase in pulmonary vascular resistance (26,27). This decrease in heart rate may be mediated by H₃ receptors (16). The longer temporal progression of the changes in respiration and pulmonary mechanics indicate the involvement of mediators and mechanisms other than those that caused the marked cardiovascular responses.

The site(s) of bronchoconstriction cannot be ascertained from these studies and likely differs between the bronchial and alveolar deposition patterns. There is some evidence that the effect of histamine on smooth muscle tone in the lungs is primarily peripheral rather than central (28). The results of studies by Nadel et al. (29) indicate that the principal

sites of constriction were the alveolar ducts and small bronchioles. Histamine-induced contraction of smooth muscle is mediated by H₁ receptors (30), which have been shown to be present in the peripheral lung (31).

Initially, whether administered by aerosol to the alveolar or bronchial regions of the lungs, histamine-induced bronchoconstriction appeared to follow a time course for peak response similar to those demonstrated by others (32), with a somewhat more rapid recovery. Although similar doses of predominantly bronchial and alveolar histamine resulted in similar magnitudes of the peak responses of R_L and RR, the high bronchial histamine dose caused a greater and prolonged change in C_{dyn}, P_{CO₂}, and R_L. Between 10 and 30 min, MV was greater for alveolar than for bronchial histamine, which may have contributed to the faster improvement in P_{CO₂} levels after alveolar histamine. The prolonged increase in R_L was presumably due to the high concentration/surface area activating H₁ receptors on bronchial smooth muscle (30). The increase in R_L due to alveolar deposition of histamine was predominantly caused via activation of pulmonary C fibers, which through a reflex transmitted via the vagosympathetic trunks mediated the constriction of smooth muscle in the airways and alveolar ducts, whereas the increase in R_L following bronchial deposition of histamine

likely was caused by the combined effects of histamine acting directly on smooth muscle (30) and local reflex pathways (20). The decreases in C_{dyn} appeared greater for bronchial than for alveolar histamine. Following bilateral section of the vagosympathetic trunks, the decreases in C_{dyn} with bronchial and alveolar histamine were attenuated in all but one dog. A lack of correlation between *in vivo* and *in vitro* responses to histamine on smooth muscle (33) could be explained by our observation that the responses mediated by histamine effector actions are at different sites within the lungs.

To our knowledge no one has followed the ventilatory and bronchoconstrictive responses to histamine on a breath-by-breath basis for as long a length of time as in our studies (up to 90 min). We were able, therefore, to detect physiologic responses with respect to bronchial versus alveolar deposition of histamine throughout this extended time course. There was a prolonged secondary rise in R_L , indicating that histamine caused the release of a secondary bronchoconstriction-inducing mediator, an effect that was more prominent following bronchial histamine than alveolar histamine delivery. This secondary rise after bronchial histamine was abolished after bilateral transection of the vagosympathetic trunks. The secondary rise in RR and MV with alveolar histamine but not with bronchial histamine suggests that a histamine initiated release of a secondary mediator, which stimulated pulmonary C fibers. This latter increase in RR was ablated by nedocromil, suggesting that nedocromil either inhibited the release of this mediator or desensitized pulmonary C fibers.

Nedocromil sodium had effects on the physiologic responses to histamine, some of which are consistent with an inhibition of activation of sensory nerves, as demonstrated by the dose-dependent inhibition of RR. The inhibition by nedocromil of the delayed changes in RR, R_L , and C_{dyn} could be due to its inhibition of mobilizing inflammatory cells, secondary mediator release, plasma extravasation, or C-fiber desensitization (34). The histamine-induced increase of P_{CO_2} observed at the lowest dose of nedocromil was attenuated in a dose-dependent manner at higher nedocromil doses despite dose-dependent decreases in RR and MV, suggesting that nedocromil decreased the proposed ventilation and perfusion mismatch by inhibiting the release of mediators (or by central inhibition of a tonic efferent pathway regulating pulmonary vasomotor tone). However, the initial decreases in C_{dyn} were not attenuated by nedocromil and were even prolonged. Similarly, the increases in R_L were not as greatly attenuated at higher nedocromil doses as at the lowest dose.

Nedocromil has been reported to stimulate C fibers (35) and to inhibit responses due to the stimulation of sensory nerves (36). Possibly nedocromil desensitized sensory fibers for increases in both respiratory rate and sensory nerves responsible for inhibiting reflex bronchodilation.

It is remarkable that despite the difference in surface area between the bronchial and alveolar regions (300×), similar masses of capsaicin deposited in each of these regions produced similar stimulations of ciliary beat frequency (13) and that similar masses of histamine deposited in each of these regions produced the remarkably similar physiologic responses reported herein. Neither of these physiologic responses can be traced to common systemic origin. Total lung doses of approximately 185 µg histamine did not stimulate tracheal ciliary beat frequency, whereas 57 µg delivered to the lungs of baboons caused a delayed stimulation of tracheal ciliary beat frequency (37). These data suggest that this stimulation may only be observed at histamine doses below that at which bronchoconstriction occurs. Alternatively, these dogs may have been under deeper anesthesia than the baboons, resulting in a greater barbiturate-related attenuation of the hypothesized reflex. That sectioning of the vagosympathetic trunks did not effect CBF_t is consistent with our previous data showing that neither nicotinic ganglionic blockade nor muscarinic antagonism decreased the basal CBF_t (38).

Thus, a primary role of histamine is to increase respiratory rate through vagally transmitted afferent pathways, whether it is released in the bronchial mucosa or alveolar interstitium to counteract the increase in bronchomotor tone and decreased gas exchange. The histamine-induced increase in lung resistance appears to have different origins depending on the site of action (release): in the alveoli the increased bronchomotor tone appeared due to reflexes transmitted via the vagosympathetic trunk and in the bronchi due to direct constriction of smooth muscle and local reflexes. Histamine transported to the blood does not play a major role in bronchoconstriction but does in cardiovascular responses, especially in the induction of hypotension. The latter is caused by systemic vasodilation, pulmonary vasoconstriction, and decreased cardiac output. Histamine in the airways initiates secondary responses in bronchomotor tone that are maximal after 45 min. Nedocromil attenuates the increases in respiratory rate and lung resistance. In addition, it abolishes the secondary increases in bronchomotor tone.

These studies demonstrate precipitous decreases in cardiovascular function as soon as 1 min after inhalation of minute masses of ragweed allergen and suggest that these are

induced from deposition of the allergen in both the bronchial and alveolar regions of the lungs. Although histamine can mimic many of the responses associated with anaphylaxis, consistent with the reports of other investigators, it does not appear to account for all of the allergen-induced anaphylactic responses.

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